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Barbara S. Hulka, Chairman, University of North Carolina, Chapel Hill, North Carolina
Olav Axelson, University Hospital, Linkoping, Sweden
Joseph Brain, Harvard School of Public Health, Boston, Massachusetts
Patricia Buffler, University of Texas at Houston, Houston, Texas
A. Sonia Buist, Oregon Health Sciences University, Portland, Oregon
Dietrich Hoffmann, American Health Foundation, Valhalla, New York
Brian Leaderer, Yale University, New Haven, Connecticut
Genevieve Matanoski, Johns Hopkins University, Baltimore, Maryland
James Robins, Harvard School of Public Health, Boston, Massachusetts
John Spengler, Harvard School of Public Health, Boston, Massachusetts
Nicholas Wald, Medical College of St. Bartholomew's Hospital, London, England
Major contributions were also made by Drs. Devra Lee Davis, Diane K. Wagener and Marvin Schneiderman from the National Research Council.

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Increased Risk of Lung Cancer in Non-smokers Married to Smokers: A Result of ETS Exposure or of Bias?

P. N. Lee

Summary

Combined evidence from at least 15 epidemiological cohort and case-control studies appears to indicate non-smokers married to smokers have a risk of lung cancer 30%–40% higher than that of non-smokers married to non-smokers. This increase is surprisingly large, given the very low level of exposure to smoke constituents of non-smokers compared with that of smokers. The possibility that it results wholly or in part from bias, rather than as a direct effect of exposure to environmental tobacco smoke (ETS), must be considered seriously. Weaknesses of much of epidemiological evidence and the various possible sources of bias are discussed in detail.

One serious potential source of bias arises if even a small proportion of smokers are misclassified as non-smokers. Data from a series of studies specifically designed to determine accuracy of statements on current smoking habits (by salivary cotinine measurements) and on past smoking habits by repeated questionnaires) suggests that such misclassification might cause bias large enough to explain a major part, and perhaps all, of the apparent increase in lung cancer risk related to spouse smoking. Whilst evidence from a detailed review of the available literature on misclassification of smoking habits, is consistent with this view, there is a need for more research on this issue. Future epidemiological studies on passive smoking and lung cancer need to obtain more objective and reliable information on the subject's smoking habits and exposure to ETS. Bias can also arise if positive studies are more likely to be reported than negative studies and research is needed to attempt to estimate the extent of this bias.

Data currently available do not permit reliable conclusions to be drawn concerning the relationship of ETS exposure to lung cancer risk.

The Association

Since the early studies of Hirayama (1981) and Trichopoulos et al. (1981) reporting that never smokers married to smokers have a higher risk of lung cancer than those married to non-smokers, further epidemiological evidence has accumulated. Table 1 summarizes evidence from 16 published studies, 1–3 being prospective studies and 4–16 case-control studies. Wald et al. (1986), based on results from studies 1–13, reported an overall significant relative risk of 1.35, with 95% confidence limits of 1.19–1.54. This estimate is in broad agreement with other estimates of 1.30 (Lee 1984), 1.41 (Wells 1986) and 1.2–1.5 (Doll 1986). It would not be materially affected by including results from studies 14–16 of Table 1 since they are all small, and have relative risks that vary either side of the average.

While the overall evidence, which is based on a total of almost 1,200 lung cancer deaths in never smokers, predominantly in females, suggests a statistically significant

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Table 1. Summary of epidemiological studies of risk of lung cancer in never smokers in relation to environmental tobacco smoke exposure

Study number	Authors	Study location	Sex	Number of lung cancers[a]	Relative risk	Significance[b]
1	Hirayama (1981, 1984)	Japan	F	163	1.63	Yes
			M	64	2.25	Yes
2	Garfinkel (1981)	USA	F	153	1.17	No
3	Gillis et al. (1984)	Scotland	F	8	1.00	No
			M	6	3.25	No
4	Trichopoulos et al. (1981, 1983)	Greece	F	77	2.11	Yes
5	Chan and Fung (1982)	Hong Kong	F	84	0.75	No
6	Correa et al. (1983)	USA	F	22	2.07	(Yes)
			M	8	2.00	No
7	Buffler et al. (1984)	USA	F	41	0.78	No
			M	11	0.52	No
8	Kabat and Wynder (1984)	USA	F	24	0.79	No
			M	12	1.00	No
9	Koo et al. (1984, 1987)	Hong Kong	F	88	1.64	No
10	Garfinkel et al. (1985)	USA	F	134	1.31	(Yes)
11	Akiba et al. (1986)	Japan	F	94	1.50	No
			M	19	1.80	No
12	Lee et al. (1986)	England	F	32	1.00	No
			M	15	1.30	No
13	Pershagen et al. (1987)	Sweden	F	67	1.20	No
14	Wu et al. (1985)	USA	F	29	1.20	No
15	Ziegler (in Delager et al. (1986))	USA	M	16	<1	No
16	Humble et al. (1987)	USA	F	20	1.80	No
			M	8	>1.80	No

[a] Among never smoking subjects
[b] Yes = significant at 95% confidence level in comparison of exposed and non-exposed subjects; (Yes) = significance only in trend analysis or in subjects exposed to heavy smokers

association, it is not at all clear that it represents a causal effect of exposure to environmental tobacco smoke.

Before coming to any conclusion it is necessary to consider two important questions:

(a) Is the magnitude of the association plausible, in view of what is known about the epidemiology of active smoking and the relative levels of smoke constituents to which smokers and non-smokers are exposed?

(b) Is the epidemiological evidence open to any serious bias which might affect relative risk estimates in specific studies, or generally?

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Table 2. Comparison of relative risks of lung cancer in relation to passive and active smoking

Study number	Authors	Sex	Relative risk		Ratio of excess risk
			Passive	Active	
1	Hirayama (1981, 1984)	F	1.63	3.81	0.22
		M	2.25	4.91	0.32
3	Gillis et al. (1984)	F	1.00	1.53	0.00
		M	3.25	5.92	0.46
4	Trichopoulos et al. (1981, 1983)	F	2.08	2.90	0.57
5	Chan and Fung (1982)	F	0.75	3.07	−0.12
6	Correa et al. (1983)	F	2.07	18.51	0.06
		M	2.00	18.27	0.06
7	Buffler et al. (1984)	F	0.78	5.37	−0.05
		M	0.52	5.26	−0.11
9	Koo et al. (1984, 1987)	F	1.64	3.80	0.23
11	Akiba et al. (1986)	F	1.50	3.36	0.21
		M	1.80	3.55	0.31
12	Lee et al. (1986)	F	1.00	4.75	0.00
		M	1.30	12.91	0.03
14	Wu et al. (1985)	F	1.20	4.50	0.06

Plausibility

Table 2 compares relative risks of lung cancer in relation to passive and active smoking. The passive smoking estimates compare risk in never smokers according to whether or not they are married to a smoker, while the active smoking estimates compare ever smokers and never smokers. Exceptionally, in studies 1 and 3, the comparison is in relation to current rather than ever smoking. The table also shows the ratio of excess risk in relation to passive and active smoking. Nine of the 16 ratios suggest an effect of passive smoking 6% or less than that of active smoking, while seven suggest an effect 20% or more. Overall the epidemiological data appear to be indicating that passive smoking has 10–15% of the effect of active smoking. Most studies of active smoking suggest a linear relationship between lung cancer risk and number of cigarettes smoked per day, though a quadratic relationship has been proposed (Doll and Peto 1978). It follows that if the epidemiological data are unbiased one would expect that the average dose received from passive smoking is at least 10%–15% of that from active smoking.

Many workers have used the (virtually) tobacco specific marker cotinine as an indicator of exposure of passive and active smokers. Table 3, based on an extensive UK study by Lee (1987) which will be referred to in more detail below, found that the increase in salivary cotinine in relation to passive smoking was less than 1% of that in relation to active smoking. Similar findings have been reported by other workers (e.g. Jarvis et al. 1984). The only study reporting relative levels much higher than this (Matsukura et al. 1984) has been questioned (Adlkofer et al. 1985; Pittenger 1985).

Since lung cancer risk in smokers is generally thought to be related to particulate matter rather than nicotine, it can be argued that an index of relative exposure of passive

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Table 3. Salivary cotinine levels in relation to active and passive smoking

Exposure	Sex	Salivary cotinine (ng/ml)		
		Exposed	Non-exposed	Differences
Active smoking	M	319.2	0.85	318.3
	F	310.6	0.40	310.2
Spouse smoking (among non-smokers)	M	2.9	0.6	2.3
	F	1.0	0.3	0.7
Ratio of differences		Male 0.7%		
		Female 0.2%		

Table 4. Smoking related particulate levels in US smokers and non-smokers

Measure	Sex	Smoking related particulates (mg/day)		
		Active smoker	Non-smoker	Ratio
Inhaled dose	M	477.3	0.63	0.1%
	F	366.5	0.30	0.1%
Retention		80%	11%	
Retained dose	M	381.8	0.069	0.02%
	F	293.2	0.033	0.01%

and active smokers based on particulate matter would be more relevant. Table 4, based on Arundel et al. (1986), gives estimates for the US population of relative inhaled and retained particulate matter doses of non-smokers and active smokers. The ratios in Table 4 have to be adjusted upwards by a factor of 2 or 3 to make them comparable with the data in Tables 2 and 3, since (see Table 3) the difference between exposed and non-exposed non-smokers is two to three times the average level of non-smokers. This brings the inhaled dose estimates broadly in line with the cotinine estimates, though the retained dose estimates are about an order of magnitude lower. The lower figure for retained particulate matter is based on the work of Hiller et al. (1982a,b) who found that the collection efficiency of particles in environmental tobacco smoke is 11%, in contrast to the substantially higher figure of 80% for mainstream smoke. Robins (1986) also calculated that non-smokers take in the equivalent of an extremely small number of cigarettes per day in terms of respirable particulates. He noted that estimates of cigarette equivalents based on cotinine may be misleadingly high, since, whereas nicotine is in the particulate phase in mainstream smoke and will be absorbed mainly through the lungs, nicotine in ETS is mainly in the vapour phase, and, being water soluble, can be absorbed through the mucous membranes without ever reaching the lungs.

There appears to be a *huge discrepancy*, of two or perhaps three orders of magnitude between the claimed relative effects of passive and active smoke exposure and the much smaller relative exposure of passive and active smokers. What might explain this huge discrepancy?

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One might argue that studies of active smoking, by including exposed and non-exposed non-smokers in their comparison group, underestimate the effect of active smoking so that the ratios in Table 2 are too high.

This is irrelevant for three reasons:

(a) the comparison between Tables 2 and 3 is in fact direct and not affected by this false baseline problem,
(b) failure to take the false baseline into account would have virtually no effect if risk was proportional to exposure and exposures in passive smokers are so low and
(c) it ignores a bias in the opposite direction due to failure to take into account the fact that smokers obviously have greater passive smoke exposure than do non-smokers.

Another point to be considered is duration of smoking. Since, in active smokers, risk of lung cancer is approximately related to the 4th power of duration of smoking (Doll and Peto 1978), one might infer that failure to take account of differences in duration might cause relative bias by a factor of 3.2 ($= 60_4/45_4$) when comparing a 60 year old non-smoker exposed to passive smoke from birth and a 60 year smoker who started at age 15. Actually, the relative bias will be much less than this for two reasons. First, by no means all passive smokers will have been exposed since birth. Second, the "duration to a power" formula is only a valid approximation at smoker doses. Assuming a multistage model, it can easily be shown that at low doses the excess risk in relation to passive smoking becomes approximately linearly related to duration of smoking.

Neither of the above points really affect the huge discrepancy for which an explanation is being sought. If one is still wishing to accept the epidemiology as valid, one would have to seek an explanation either in a greater toxicity of ETS than mainstream smoke or in a greater susceptibility of non-smokers. While there is evidence that sidestream smoke has higher concentrations of some toxic chemicals than mainstream smoke, the relevance of this finding to environmental tobacco smoke which is aged, vastly diluted, chemically altered sidestream smoke, is not at all clear. There does not appear to be any direct evidence that ETS is particularly noxious. Nor is there any direct evidence that active smoking reduces susceptibility to relevant effects of ETS.

Limitations of Epidemiology

While it is not possible to completely rule out such explanations, the obvious alternative explanation – that the epidemiology is in some way biassed – seems on the face of it much more plausible. While the claimed effect of passive smoking may be large when viewed against the magnitude of effect predicted on dosimetric grounds, it is actually quite small when viewed against the magnitude of effect it has proved possible in the past to reliably identify using epidemiological methods. Alderson (1983) has suggested that a well designed case-control study should be able to confirm a two fold difference in risk but that, for differences less than this, the power of the study design may be inadequate. While case-control studies are particularly susceptible to a variety of sources of potential bias, this conclusion may well be true for any non-randomised epidemiological study (Lee 1988a).

In trying to assess whether bias might have arisen in the epidemiological evidence it is necessary to consider potential limitations of the available data. A number of general points can be made:

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